Intracellular pH measured by ^{31}P MR-Spectroscopy predicts site of progression in recurrent glioblastoma under antiangiogenic therapy with bevacizumab.

Katharina Johanna Wenger[1], Oliver Bähr[1], Elke Hattingen[2], and Ulrich Pilatus[2]
[1]*Neurooncology, Goethe-University Frankfurt, Frankfurt, Hessen, Germany,* [2]*Neuroradiology, Goethe-University Frankfurt, Frankfurt, Hessen, Germany*

Purpose: In solid tumors, major changes in the expression and/or activity of plasma membrane ion pumps and transporters facilitate proton efflux and enable tumor cells to maintain a higher intracellular pH (pHi), while the microenvironment (pHe) is commonly more acidic compared to normal differentiated adult cells. An alkaline pHi supports various mechanisms involved in cellular proliferation and limits apoptosis, therefore promoting cell survival. We proposed that these early changes in pH take place before an MR-detectable recurrence occurs. To prove our hypothesis, we employed in-vivo ^{31}P MR spectroscopic imaging (MRSI) in patients with recurrent glioblastoma (rGBM) before and under antiangiogenetic therapy (bevacizumab, BEV) until tumor progression.

Methods: At our institution we prospectively enrolled 83 patients with recurrent glioblastoma or gliosarcoma that were treated with BEV. All patients received a full baseline and 8-weeks-follow up MRI and ^{1}H/^{31}P MRSI until further progression. According to the predefined criteria by Pope et al.[1] for distant or diffuse tumor progression, 14 patients of this group were selected based on their tumor progression patterns at time of on-study progression (subsequent tumor). An area of interest for voxel selection on baseline MRSI data was defined retrospectively at the site of the subsequent tumor (Figure 1, row 3, frontal selection marks control, parieto-occipital selection marks subsequent tumor). The area of interest showed no detectable lesions before BEV on standard MRI sequences (Figure 1, upper row left).

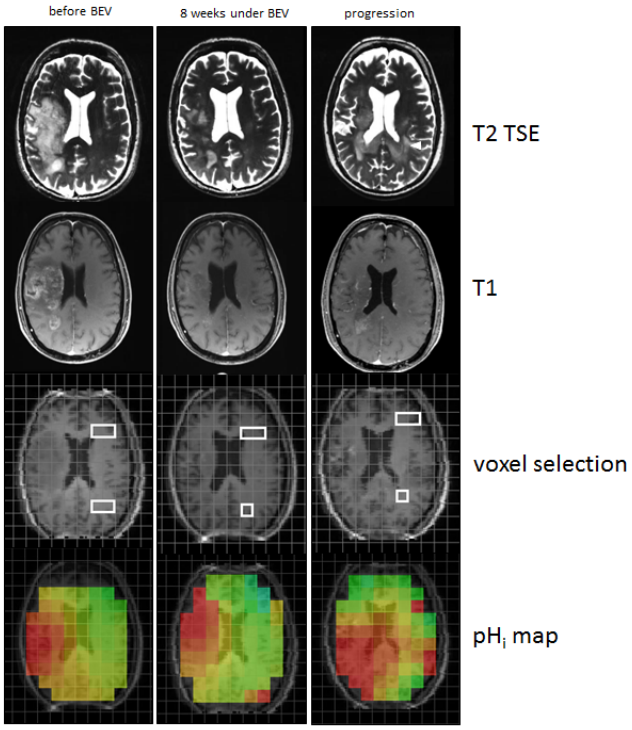

Figure 1

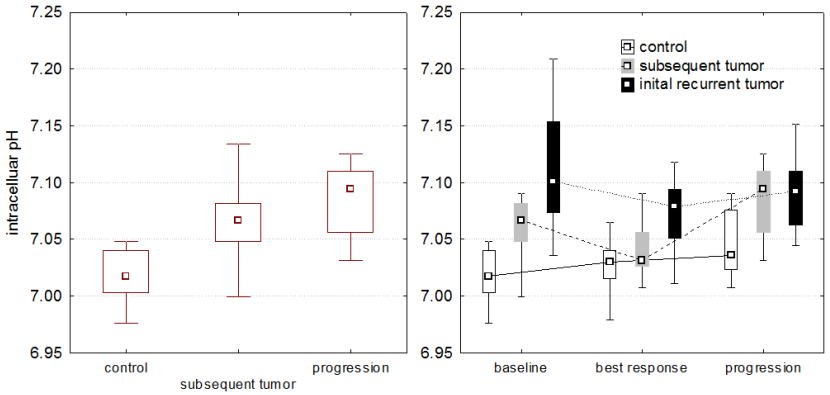

Figure 2

Results: The pHi in the area of interest (subsequent tumor) was significantly higher than the pHi of the contralateral normal appearing tissue (control) ($p < 0.001$) and similar to the pHi of the existing tumor (Figure 2, left panel). The pHi decreased at time of best response (8 weeks-follow up, $p = 0.11$), followed by an increase upon further progression (Figure 2, right panel, $p = 0.03$), which has been previously described for the initial tumor site.[2] Only at the time point of subsequent progression this hitherto invisible tumor was detectable on standard MRI sequences.

Conclusion: Elevated pHi in radiographically normal appearing tissue at baseline can predict the site of subsequent progression in patients with recurrent glioblastoma treated with BEV. As hypothesized above, the observed pHi changes precede T1 or T2 detectable lesions and may promote growth of the subsequent tumor.

References:

1. Pope WB, Xia Q, Paton VE, et al. Patterns of progression in patients with recurrent glioblastoma treated with bevacizumab. Neurology. 2011 Feb 1;76(5):432-7
2. Ulrich Pilatus, Veronika Völker, Oliver Bähr, et al. P MR spectroscopy shows pH-changes in recurrent glioblastomas during antiangiogenic therapy, Proc. Intl. Soc. Mag. Reson. Med. 22 2014, 3351